Catalysis Communications 55 (2014) 70–73

Contents lists available at ScienceDirect

Catalysis Communications

journal homepage: www.elsevier.com/locate/catcom

Short Communication

[bmIm]OH catalyzed hetero-cyclisation of o-halobenzoic acid and alkyne: A green approach to synthesize isocoumarins

Malik A. Waseem, Shireen, Afaf A. Abumahdi, Arjita Srivastava, Anjali Srivastava, Rahila, I.R. Siddiqui *

Laboratory of Green Synthesis, Department of Chemistry, University of Allahabad, Allahabad 211002, India

ARTICLE INFO

Article history:
Received 17 April 2014
Received in revised form 10 June 2014
Accepted 11 June 2014
Available online 21 June 2014

Keywords:
Basic ionic liquid ([bmImOH])
Isocoumarin
Heterocycle Green Protocol
Ambient conditions

ABSTRACT

Efficient and environmentally benign heterocyclization of o-halobenzoic acid and alkyne has been developed using [bmIm]OH as green catalyst. This methodology offers a metal and base free approach and is endowed with mild reaction conditions, high yields and better functional group tolerating ability. The recyclability and reuse of [bmIm]OH add the methodology a wide scope.

1. Introduction

Recent advancement of ionic liquids (ILs) as catalyst, solvent and base has opened new vistas in the field of synthetic chemistry research [1–3]. A wide range of heterocycles including spirothiazines, indolizines, quionolines, and many more vital heterocycles have been synthesized using this approach [4–6]. The growing attention of ionic liquids is by their tuneable features like complete recovery, reusability, negligible vapor pressure, wide solvating capability, multiple bond forming efficiency and many other green credentials such as alternative reaction media to molecular solvents, catalysts and reagents [1–3]. Recently our research group has developed [bmIm]OH catalyzed intramolecular heterocyclization leading to the synthesis of biologically recognized substituted benzofuran derivatives [7]. Continuing our work on ionic liquid promoted heterocycle synthesis, we decided to develop eco-compatible ionic liquid promoted strategy for the synthesis of biologically recognized isocoumarins.

Isocoumarins are an elite class of heterocyclic compounds with astounding biological significance. Anti-cancer, anti-hypertensive, anti-clotting, hepatoprotective, and anti-viral activities are prominent among them [8–15]. In addition, isocoumarin derivatives are useful precursors for the synthesis of various natural products, these natural products have an immense scope in the biological world. Thus because of strong requirement of 3, 4-disubstituted isocoumarins in medicament and natural product synthesis, a number of methods are available in literature for the construction of isocoumarin derivatives. However, most of the reported methodologies have drawbacks, which include, use of expensive and hazard catalysts such as copper(II)chloride, indium(III)chloride, bismuth(III)nitrate-penta hydrate, ruthenium, palladium and rhodium [16–23]. Further carcinogenic volatile organic solvents (VOLs), complex starting materials, and drastic reaction conditions remained the scientific challenge. Therefore an easy, eco-friendly and practical method for the synthesis of isocoumarin derivatives would be highly desirable and useful at present.

To circumvent the above mentioned drawbacks for the construction of isocoumarins as well as in continuation of our research program for the development of simple, versatile synthetic methodology for biodynamic heterocyclic scaffolds, [24–35] herein we report a simple and highly efficient strategy for the synthesis of 3,4 isocoumarin derivatives by [bmIm]OH catalyzed addition of o-halobenzoic acids to internal alkyne (Scheme 1).

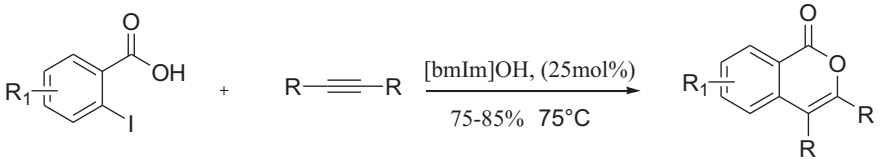
In this reaction O – C and C – C bonds were formed simultaneously to afford isocoumarins in moderate to good yields. The synthesized core moiety is well tolerated by diverse functional groups (Table 3). These functional groups were easily converted to useful functional groups that produce drug like library of compounds and add the applied methodology a wide scope.

Initially the reaction was performed by using o-iodobenzoic acid and the symmetrical alkyne, (DMAD) as model reactants in 25 mol% of basic ionic liquid, ([bmIm]OH) as solvent and catalyst. After 3 h of stirring, the reactants were transformed into products. The analysis of spectral data ^{1}H NMR, ^{13}C NMR, and MS supported the formation of isocoumarin. The formation of the product prompted us to optimize the reaction conditions.

To explore the generality of the applied strategy and to obtain 100% product yield in a shorter reaction time, we attempted to investigate the

* Corresponding author.
E-mail address: dr.irsiddiqui@gmail.com (I.R. Siddiqui).

http://dx.doi.org/10.1016/j.catcom.2014.06.010
1566-7367/



Scheme 1. Synthesis of 3, 4 substituted isocoumarins.

optimization of the reaction conditions with regard to, different solvents, bases, temperatures and reaction times using previously employed $CuCl_2$ catalyst with o-iodobenzoic acid and dimethylacetylenedicarboxylate, (DMAD) as model substrate for the representative compound **4a** (Table 1).

Results show that in case of solvent CH_3CN and base (NaOH), 61% yield was obtained at 100 °C (Table 1, entry 2). But in the case of other solvents and bases, the yield of the product was only 35–47% (Table 1, entries 1, 3–9). However the reaction did not give any desired product **4a** in the absence of catalyst $CuCl_2$ or base (Table 1, entry 10, 11). Surprisingly when the model reaction was carried in [bmIm]OH at 75 °C for 7 h the desired product were obtained in an excellent yield of 85% (Table 1 entry 12). However when the model reaction was carried out at room temperature, low yield of 27% was obtained (Table 1, entry 13).

In order to make the reaction conditions precise and accurate, which is very useful for practical point of view, the optimum catalyst loading of [bmIm]OH was investigated. It was observed that best results were obtained when the 25 mol% of [bmIm]OH was used (Table 2, entry 5). From 5 mol% to 25 mol% yield of product accordingly increases. After increasing mol% from 25 mol% to 35 mol%, no change in product yield was determined (Table 2, entries 6 and 7).

With the optimized reaction condition in hand, the scope of the tandem heterocyclization was also explored. A variety of 2-iodobenzoic acid derivatives with symmetric alkynes were initially examined. The results were summarized in (Table 3). However when internal alkynes and unsymmetrical alkynes were carried under standard reaction conditions unfortunately no product formation was observed (Table 3 entry 11, 12). The electronic effect was also studied. Reactants containing electron-withdrawing groups performed moderately better under the optimized reaction condition than their corresponding electron donating counterparts. It is noteworthy that when substrates with electron-releasing groups were used, the reaction required a longer time compared to substrates bearing electron-withdrawing groups (Table 3).

The reaction is most likely initiated by abstraction of hydrogen from carboxylic OH group of 2-iodophenol by hydroxide anion of [bmIm]OH to produce carboxylate anion, then probably the additive attack of generated carboxylate nucleophile on highly reactive triple bond of dimethylacetylenedicarboxylate (DMAD) whose electrophilicity is further enhanced by the electrostatic attraction of imidazole ring of [bmIm]OH. The final step is the removal of iodine from benzene by generated anion leading to facile heterocyclization under the synergetic effect of ionic liquid to form isocoumarin (Scheme 2). This proposed reaction mechanism is very simple, [bmIm]OH acts both base and promoter of the reaction. Further [bmImOH] was easily regenerated and reused which is better explained in an experimental section.

The reaction scope was further enhanced, when [bmIm]OH was recycled and reused. Recycling and reuse was done four times, the best thing which was exciting, the small loss of product yield was observed after each recycle (Fig. 1).

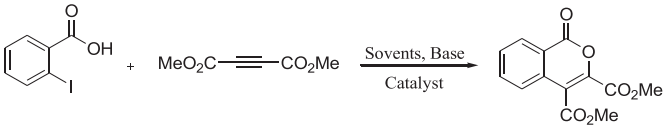
2. Conclusion

One-pot two-component novel, [bmIm]OH promoted methodology for the synthesis of isocoumarin derivatives has been devised. The applied methodology offers wide superiority over the existing, in terms of product yield, reaction time, diverse functional group tolerance and use of nonhazardous nature of reagents. Recyclability and reuse of [bmIm]OH after the reaction completion add the methodology a wide scope.

Acknowledgment

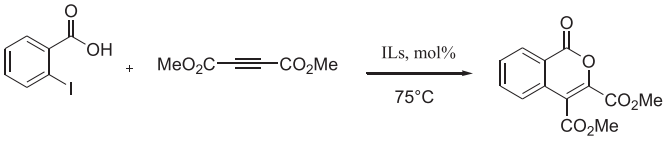
Malik Abbdul Waseem and Shireen Siddiqui gratefully acknowledge University Grants Commission (UGC) New Delhi for research grant in the form of project and as senior research fellow (SRF). We are also thankful to the Department of Chemistry, University of Allahabad for academic facilities. The authors would also like to thank SAIF, Chandigarh for spectral analysis.

Table 1
Influence of various solvents, bases and Temperature in presence of $CuCl_2$ on synthesis of **4a**.



Entry	Catalyst	Base	Solvent	T °C	Time (h)	Yield (%)
1	$CuCl_2$	$N(Et)_3$	CH_3CN	100	8	37
2	$CuCl_2$	NaOH	CH_3CN	100	6	61
3	$CuCl_2$	Cs_2CO_3	CH_3CN	RT	8	42
4	$CuCl_2$	$N(Et)_3$	EtOH	RT	9	39
5	$CuCl_2$	NaOH	EtOH	75	8	44
6	$CuCl_2$	Cs_2CO_3	EtOH	RT	8	40
7	$CuCl_2$	$N(Et)_3$	DCM	100	9	41
8	$CuCl_2$	NaOH	DCM	100	8	45
9	$CuCl_2$	Cs_2CO_3	DCM	RT	9	35
10	–	NaOH	CH_3CN	87	9	0
11	$CuCl_2$	–	CH_3CN	RT	9	0
12	–	–	[bmIm]OH	75 °C	7	85
13	–	–	[bmIm]OH	RT	7	27

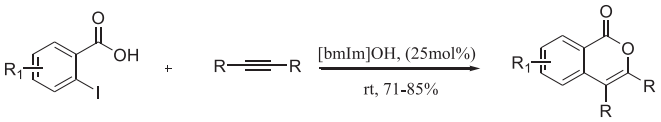
Table 2
Influence of mol% of [bmIm]OH on **4a**.

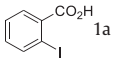
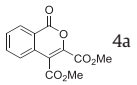
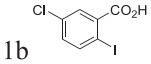
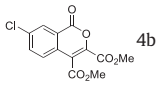
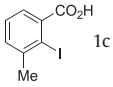
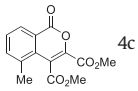
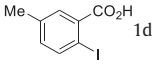
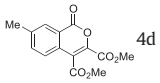
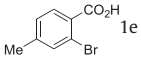
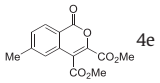
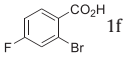
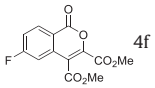
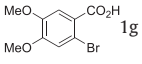
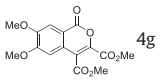
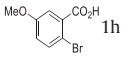
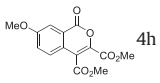
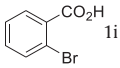
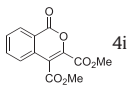
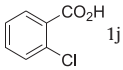
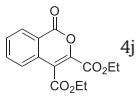
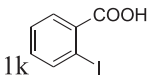
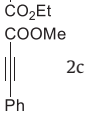
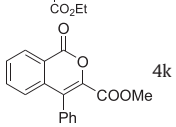
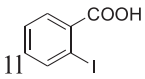
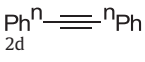
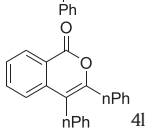


Entry	Mol% of [bmIm]OH	Time	Yield%
1	5	9	41
2	10	8	53
3	15	6	63
4	**25**	**5**	**85**
5	30	5	85
6	35	5	85

Bold values indicates the optimized reaction condition where maximum yield was obtained.

Table 3
[bmIm]OH promoted synthesis of 5(a-l).



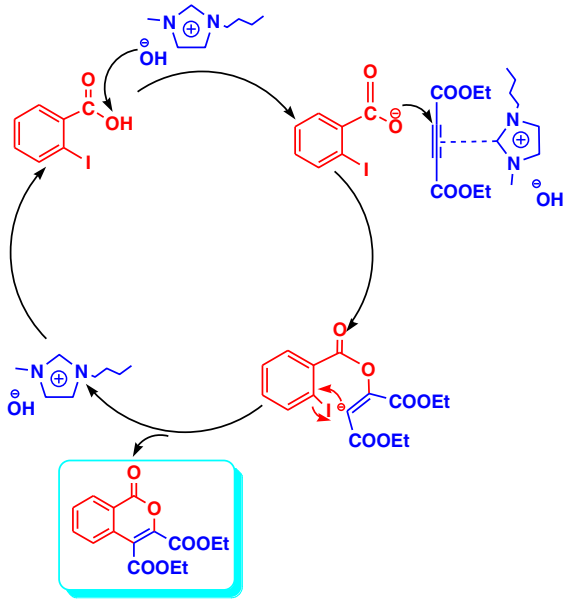
Entry	o-Halobenzoic Acid	Alkyne derivatives	4 (a-i)	Time (h)	Yield (%)
1	 1a		 4a	7	83
2	 1b	 2a	 4b	7	85
3	 1c	 2a	 4c	8	83
4	 1d	 2a	 4d	8	83
5	 1e	 2a	 4e	8	85
6	 1f	 2a	 4f	7	85
7	 1g	 2a	 4g	5	83
8	 1h	 2a	 4h	6	83
9	 1i	 2a	 4i	6	77
10	 1j	 2b	 4j	7	75
11	 1k	 2c	 4k	9	0
12	 1l	 2d	 4l	9	0

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2014.06.010.

References

[1] T. Welton, Chem. Rev. 99 (1999) 2071–2084.
[2] P. Wasserchеid, W. Keim, Angew. Chem. Int. Ed. 39 (2000) 3772–3789.
[3] R. Sheldon, Chem. Commun. (2001) 2399–2407.
[4] X. Wang, M. Zhang, H. Jiang, C. Yao, S. Tu, Tetrahedron 63 (2007) 4439–4443.
[5] A. Dandia, R. Singh, D. Saini, J. Chem. Sci. 125 (2013) 1045–1053.
[6] J. Peng, Y. Deng, Cuihua Xuebao 22 (2001) 598; Chem. Abstr. 136 (2002) 218602.
[7] I.R. Siddiqui, M.A. Waseem, S. Shamim, Shireen, Arjita Srivastava, Anjali Srivastava, Tetrahedron Lett. 54 (2013) 4154–4158.
[8] W. Zhang, K. Krohn, S. Draeger, B. Schulz, J. Nat. Prod. 71 (2008) 1078.
[9] D. Engelmeier, F. Hadacek, O. Hofer, G. Lutz- Kutschera, M. Nagl, G. Wurz, H. Greger, J. Nat. Prod. 67 (2004) 19.
[10] J.H. Lee, Y.J. Park, H.S. Kim, Y.S. Hong, K.W. Kim, J.J.J. Lee, Antibiotics 54 (2001) 463.
[11] H. Matsuda, H. Shimoda, M. Yoshikawa, Bioorg. Med. Chem. 7 (1999) 1445.
[12] A.C. Whyte, J.B. Gloer, J.A. Scott, D.J. Mallock, Nat. Prod. 59 (1996) 765.
[13] J.J. Heynekamp, L.A. Hunsaker, V. Jagt, R.E. Royer, L.M. Decka, J. Vander, D.L., Bioorg. Med. Chem. 16 (2008) 5285.
[14] G.B. Gabriel, R. Wang, X. Liu, K.N. Nilima, A.H. Mac, T. Cihlar, C. Gibbs, S. Swaminathan, W. Lee, M. Dermott, Antimicrob. Agents Chemother. 51 (2007) 543.
[15] R.A. Carpita, F. Bellina, P. Stabile, L. Mannina, Tetrahedron 59 (2003) 2067.
[16] T. Ueura, T. Satoh, M. Miura, Org. Lett. 9 (2007) 1407.
[17] K. Ueura, T. Satoh, M. Miura, J. Org. Chem. 72 (2007) 5362.
[18] P. Zhao, D. Chen, G. Song, K. Han, X. Li, J. Org. Chem. 77 (2012) 1579.
[19] G. Zeni, R.C. Larock, Chem. Rev. 104 (2004) 2285.
[20] R.C. Larock, M.J. Doty, X.J. Han, Org. Chem. 64 (1999) 8770.
[21] R.C. Larock, E.K. Yum, M.J. Doty, K.K.C. Sham, J. Org. Chem. 60 (1995) 3270.
[22] R.K. Chinnagolla, M. Jeganmohan, Chem. Commun. (2012) 2030.
[23] L. Ackermann, J. Pospech, K. Graczyk, K. Rauch, Org. Lett. 14 (2012) 930.
[24] S. Cai, F. Wang, C. Xi, J. Org. Chem. 77 (2012) 231–236.



Scheme 2. Plausible mechanism for the formation isocoumarin derivatives.

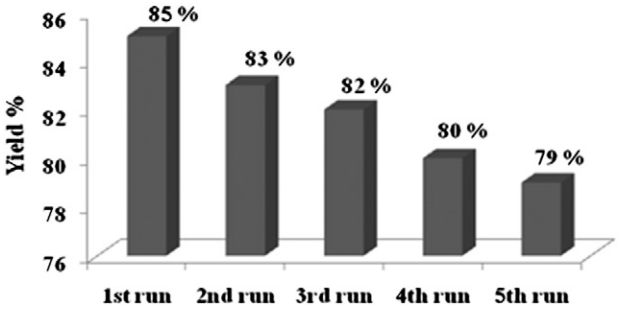


Fig. 1. Effect on product yield after each recycle and reuse of [bmIm]OH.

[25] M. Shimizu, K. Hirano, T. Satoh, M. Miura, J. Org. Chem. 74 (2009) 3478–3483.
[26] V. Subramanium, V.R. Batchu, D. Barage, M. Pal, J. Org. Chem. 12 (2005) 4778–4783.
[27] Y. Liang, Y.-X. Xie, J.-H. Li, Synthesis (2007) 400–406.
[28] R.K. Chinnagolla, M. Jeganmohan, Chem. Commun. 48 (2011) 2030–2032.
[29] S. Cai, F. Wang, C. Xi, Synthesis 44 (2012) 1892.
[30] I.R. Siddiqui, P.K. Singh, J. Singh, J. Singh, J. Agric. Food Chem. 51 (2003) 7062–7065.
[31] I.R. Siddiqui, P.K. Singh, J. Singh, J. Singh, Chem. Res. 8 (2004) 554–555.
[32] I.R. Siddiqui, S. Shamim, D. Kumar, Shireen, M.A. Waseem, New J. Chem. 36 (2012) 2209–2214.
[33] I.R. Siddiqui, Shireen, S. Shamim, A.A.H. Abumhdi, M.A. Waseem, A. Srivastava, Rahila, A. Srivastava, New J. Chem. 37 (2013) 1258–1263.
[34] I.R. Siddiqui, V. Srivastava, P.K. Singh, Nucleosides Nucleotides Nucleic Acids 27 (2008) 1532–2335.
[35] I.R. Siddiqui, A. Singh, S. Shamim, V. Srivastava, P.K. Singh, S. Yadav, R.K.P. Singh, Synthesis 20 (2010) 1613–1616.